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Detection fimH gene of *Escherichia coli* isolated from the urine of Iraqi diabetic patients with UTI and its relation with IL-6 serum levels

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Abstract

This study aims to identification of uropathogenic *Escherichia coli* from diabetic and non-diabetic patients with UTI and to detect of the fimH gene in these strains by molecular methods and to comparison the serum cytokines levels (IL-6) between diabetic and non-diabetic patients diagnosed with UTI caused by *Escherichia coli*. This study was carried out in Baghdad hospitals during the period between February to July 2022. Urine and blood samples were collected and identification of *Escherichia coli* in urine samples was done by microbiological and molecular methods, while blood samples were collected to measure IL-6 in these strains. All strains subjected to PCR for detection the presence of uidA gene and to detect the presence of fimH gene. The result of the study showed that *Escherichia coli* was the most prevalent causative pathogen and fimH gene was detected in all strains diagnosed as *Escherichia coli*. Also, The results showed that there were statistical differences in the levels of IL-6 among studied groups with means± SD (71.63± 10.69 control group, 100.60±15.47 Non-DM group, 148.70±73.81 DM group)(P value < 0.001).

Keyword: *E. coli*; Fim H gene; UTI; IL-6

1. Introduction

The urethra is the first point of entry for any potential source of infection, [1]. *Escherichia coli* drives about 80% of all UTIs, and these bacteria that are found in the urinary system are called (UPEC), there are numerous virulence factors in this UPEC that increase the pathogenicity of these strains. Type 1 fimbriae (T1F) are crucial for adherence between pathogens and host tissues [2],[3].Until soon only a few unique virulence factors can tell us the difference between pathogenic and useful E. coli but nowadays molecular typing techniques are becoming more powerful and widely available and numerous essential facts regarding microbe relations, clinical detection, reservoir and new ExPEC transfer mechanisms are brought to light by new computational methodologies [4],[5]. Microorganism invasion of the urethral and bladder results in inflammatory reactions due to urinary tract infections. As part of the host's inflammatory response, a group of pro-inflammatory cytokines are screated. This makes the inflammatory response even worse [6] Inflammation occurs when the immune system reacts to threats, including toxic compounds, damaged cells, pathogens, or radiation, by releasing inflammatory cytokines and other chemicals.Thus, inflammation serves an essential protective function in the therapy of disease. When urothelial cells are exposed to UTI-causing substances, they release interleukin 6 (IL-6), a vital component of the inflammatory response that possible exploited as a biomarkers for earlier UTI detecting[6]

Believing that *Escherichia coli* is the utmost recurring cause of UTI and interleukin-6 (IL-6) is implicated in a body's reaction to E. coli infections, a positive correlation among IL-6 release and UTI can be deduced [7]. IL-6 can play a preventive and harmful role due to its anti-inflammatory and pro-inflammatory states. This seems to be a problem because IL-6 sends signals through both the cis and trans signaling pathways. Each path has a different effect. The cis

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or classic path is restorative and protecting, while the trans path makes inflammation worse. The vulnerability of cells and the subsequent signaling cascade to circulating IL-6 differ between the routes due to the different locations of the IL-6R that connect to IL-6. The IL-6R, a transmembrane receptor, is related for a cell membrane in the cis route, where it transmits signals alongside gp130, another transmembrane protein. Hence, IL-6 initiates biological functions through binding to gp130 and the membrane-bound IL-6R. Specific leukocytes, epithelial cells, neutrophils, hepatocytes, and some monocytes are among the select few cell types expressing membrane bound IL-6R. The Trans route involves the formation of a dissolvable IL-6/sIL-6R complex that can bind to gp130 on its own once IL-6 has compelled to sIL-6R. Given that Gp130 is found on the membranes of every cell in the body, the Trans pathway response to interleukin 6 (IL-6) can be pretty robust [8]. Research on mice lacking IL-6 expression showed that they developed more acute UTIs despite developing symptoms progressively, suggesting that this balance is crucial for inducing an optimal immune response to limit infection like in UTIs [9]. IL-6 can alter glucose homeostasis and metabolic through working on skeletal muscle cells, adipocytes, hepatocytes, and neuroendocrine cells, and it can trigger death in pancreatic islets with other inflammatory cytokines [10].

It has long been recognized that type 1 (T1D) and type 2 (T2D) diabetes represent the two primarly etiologies of the illness (T2D). Type 2 diabetes (T2D) accounts for 90-95% of all instances of the illness. Generally, insulin defiance is an underlying cause, while relative insulin insufficiency is still a major contributor [11]. Multiple experimental investigations have linked inflammation and its causes to the development of type 2 diabetes. Earlier onset of T2DM has been linked to low-grade systemic inflammation, according to experimental researchs [12]. This low-grade inflammation causes higher cytokine levels, like as IL-6 [13]. It's unclear how IL-6 causes diabetes. Some research suggest IL-6 impairs insulin activity [14],[15], whereas rest believe it's needed to keep glucose homeostasis [16].

In addition to inhibiting non-oxidative glucose metabolism, IL-6 also inhibits lipoprotein lipase, which raises plasma triglyceride levels (and hence contributes to the etiology of diabetes) [17]. In contrast, IL-6 may inhibit cytokine-mediated transcriptional component activation of insulin receptor by triggering the inhibitor of cytokine signalling proteins, which were first identified as negative regulators of signalling caused by cytokines [8]. STAT5B, short for activator and signal transducer of transcription5B, is a member of the superfamily of transcription factors known as STATs. STAT5B is a signal transducer and insulin receptor transcription factor. Cytokine-receptor kinases add a phosphate group to STAT5B. STAT5B stimulates insulin transcription factor via potentiating insulin receptor tyrosine kinase. SOCS proteins limit the stimulation of insulin transcriptional activation by interacting with STAT5B. SOCS proteins inhibit insulin action, while IL-6 activates them. IL-6 is a biomarker for insulin opposition and diabetes [12] .

2. Material and Methods

2.1. Patients and Study Design

The present comparative cross- sectional study includes 191 patients with and without diabetes mellitus, their age ranging from 14-80 years who attended to Al-imamain alkazumain hospital between February - June 2022. The patients were randomly selected after diagnosis by urologist. All patients complaining of sign and symptoms of urinary tract infection. Medical records were reviewed for each patient, including: age, gender, symptoms, duration of diabetes, blood sugar, weight, length, frequency of urinary tract infection during current year, taking any antibiotic within the current infection, any other chronic diseases. The patients excluded from current study were those who were receiving antibiotics, pregnant women and patients have another clinical condition such as autoimmunity diseases, catheter in urinary system or kidney stones.

2.2. Blood Samples

Blood samples were taken from patients with sterile condition using 5 ml syringe and then the blood was divided into 2 tubes. 2 ml was transferred to EDTA tube as whole blood for measuring of HBA1C which used as proxy indicator for diabetes, 3 ml was transferred to gel tube and leaved to clot for 10 min at room temperature then centrifugate at 3000 rpm for 10 min to obtain serum which made as aliquots and these aliquots were frozen at -20C till the period of cytokines (IL-6) evaluation. This test only used for infected patients with *Escherichia coli* causing UTI.

2.3. Urine Samples

Midstream urine was gathered randomly from diabetic and non-diabetic cases of both genders (hospitalized and non-hospitalized) who were suffered from signs and symptoms of UTI. All urine specimens were gathered in the screw-cap sterile receptacles and moved to the microbiologic lab within an hour.

2.4. Estimation of HBA1c by High-Performance Liquid Chromatography (HPLC) method

HBA1C levels were measured using a D-10 instrument and the HPLC technique with 2 ml of whole blood in EDTA tubes. The D-10 relies on high-performance liquid chromatography with ion exchange to separate the analytes. Automatic sample dilution and injection into the analytical cartridge occurred on D-10. The D-10 separates the hemoglobins depending on how their ions interact with the substance in the cartridge. It does this by sending a buffer gradient with rising ions to the cartridge. After the separated hemoglobins have been cleaned, they are put using the flow cell of a filter photometer to measure the absorbance at 415 nm. Software is then used to make sense of the raw data from each analysis. The HbA2\ F\ A1c values are quantified using a 2-level calibration. Every analyzed sample also includes a chromatogram and report. The A1c peak is shaded. The Exponentially Modified Gaussian (EMG) method is employed to calculate the A1c area.

2.5. Molecular Identification of *Escherichia coli*

Polymerize Chain reaction (PCR) holds been applied as a final diagnosis for *Escherichia coli* colonies with species level classification. All colonies with a positive phenotypic identification were re-inoculated in tube with 10 ml of brain heart broth to obtain pure bacterial growth to use in DNA extraction.

2.5.1. DNA Extraction

The *Escherichia coli* chromosomal DNA extraction was carried out on entirely *Escherichia coli* isolates using Genomic DNA Extraction kit (HiMedia \ India) and according to the recommendation of manufacturing company which used the spin-column procedure.

2.5.2. Primers Preparation

The uidA gene is encoding the beta-glucuronidase enzyme gene in *Escherichia coli* species genome with 75 bp in size used as a target for molecular diagnostic by ECN 1254F (5`GCAAGGTGCACGGGAATATT 3`) and ECN 1328R (5`-CAGGTGATCGGACGCGT-3`) primers [18] as shown in (Table 1) and the primers utilized in this research were bought from the Iraqi Scientific Researcher Company, ALDiwaniyah.

Table 1 Primers of uidA gene used to identification of *Escherichia coli*

primers	Nucleotide Sequences (5´-3´)	Base pair (bp)
uidA gene (forward)	GCAAGGTGCACGGGAATATT	75
uidA gene (reverse)	CAGGTGATCGGACGCGT	75

2.5.3. Mixture and Conditions for Escherichia coli Identification

In Bio-Rad thermal cycler, the PCR was conducted with a program as described in (table 2, 3) relay on program mentioned in [18] study. The work was performed in the laminar flow cabinet and the cooled racks specific for PCR work were used.

Table 2 Mixture and Volume Preparation of *Escherichia coli* identification

Mixture and volume
12.5µl green master mix
1.25µl F primer 10 Pico mole 1.25µl R primer 10 Pico mole
5 µl DNA template/100 ng
5 µl free nucleic water
Total 25µl

Table 3 Conditions and Program of Reaction PCR for *Escherichia coli* identification

Program conditions		
stage	time	cycle
denaturing	98 C /2 min	1
denaturing	95 C/30 sec	35
Annealing	56 C/2 min	
Extension	72C/1 min	
Extension	72 C / 5 min	1

2.6. Molecular Detection of FimH gene in *Escherichia coli*

2.6.1. Primers Preparation

The primers were prepared according to [19] and the nucleotide sequence of the primers were shown in (Table 4) and purchased from the Iraqi Scientific Researcher Company, ALDiwaniyah.

Table 4 Primers Used in This Study .

primers	**Nucleotide Sequences (5´-3´)**	**Base pair (bp)**	**annealing temperature**
FimH (forward)	GTGCCAATTCCTCTTACCGTT	164	64°C
FimH (reverse)	TGGAATAATCGTACCGTTGCG	164	

2.6.2. PCR Mixture and Conditions for Detection of FimH

The PCR mixture and conditions for amplifying the fimH gene by PCR were showed in (Table 5, 6) and according to [19]

Table 5 Mixture and volume preparation of FimH identification

Mixture and volume
12.5µl green master mix
1.25µl F primer 10 Pico mole 1.25µl R primer 10 Pico mole
5 µl DNA template/100 ng
5 µl free nucleic water
Total 25µl

Table 6 Conditions and Program of Reaction PCR for FimH identification

Program conditions		
Stage	Time	cycle
denaturing	96°C /3 min	1
denaturing	96°C /30 sec	35
Annealing	64 °C /5 min	
Extension	72°C /1 min	
Extension	72 °C / 5 min	1

2.7. Evalution of Interlukine 6 (IL-6) by ELISA Technique

2.7.1. Priciple of Assay

The test was done according to its basic idea using a commercially obtainable kit and the quantitative sandwich enzyme immunoassay method. İn this study the used kit with Enzyme-Linked Immunosorbent Assay (ELISA). A Human IL6 antibody has already been used to coat the plate. When IL6 from the specimen was introduced, it stuck to the antibodies on the wells. Then biotinylated Human IL6 Antibody was placed, and IL6 in the specimen was bound to it. Then Biotinylated IL6 antibody was mixed with Streptavidin-HRP, which stuck to it. When Streptavidin-HRP is incubated, all unattached molecules are washed away during the washing process. When Human IL6 is introduced to a substrate solution, a color change occurs in direct proportion to the concentration of the protein. A stop solution containing acid is used to end the reaction, and 450 nm absorbance determines how much product was produced.

3. Results and Discusion

3.1. Description of Investigation Subgroups

The total digit of patients that were subjected for urine and blood samples were 230 samples. Diabetic patients group (DM group) was 95 (41.3%) and non-diabetic patients (Non-DM group) were 95 (41.3%). Among DM group there were 25 males (26.3%) and 70 females (73.7%). Non diabetic group included 25 males (26.3%) and 70 females (73.7%). Control group was 40 healthy people (17.4%); males were 21 (52.5%) while the females were 19 (47.5%) as shown in (Table 7).

Table 7 Description of Investigation Subgroups

Gender		**Study groups**		
		Control	DM	Non-DM
	Female	19	70	70
	%	47.5%	73.7%	73.7%
	Male	21	25	25
	%	52.5%	26.3%	26.3%
Total		40	95	95
%		100.0%	100.0%	100.0%

3.2. Culture Urine for UTI

Out of 190 urine sample that were cultured (DM and Non-DM groups), 158 were positive for bacterial growth (82.7%) and only 84 samples (53.17%) of 158 samples (44.2% of 190 samples) were positive for E. coli growth which were subjected to further investigation and 74 (46.83%) of 158 (38.95% of 190 samples) that were positive for other bacterial species as well as the rest number of 190 urine samples 32 (16.85 %) that were negative for bacterial growth did not subjected to further investigations. Control group were not subjected to urine culture because of the nature of the cases in this group is that it consists of healthy people who are not infected, and it was confirmed that there was no infection through the urine analysis, and it was confirmed that there were no pus cells in the urine . The percentage of urine bacterial culture was illustrated in (Figure 1).

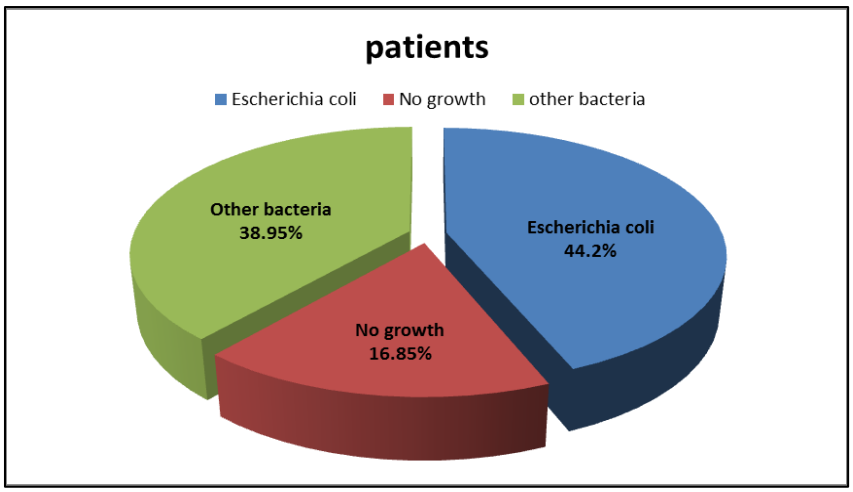

Figure 1 The Percentage of Urine Bacterial Culture.

The result of this study showed that UPEC is the most predominant pathogen among other bacteria that infect human urinary system and its prevalence was (53.1%) among all positive cultures for bacterial growth and (43.9%) among all studied samples. [20] found that the incidence of *Escherichia coli* was (49.0%) among other pathogens causing UTI and this results are slightly higher than, demonstrated that the percentage of *Escherichia coli* was (43.88%) among all isolated bacteria that cause UTI.

The negative bacterial growth in the present study may be referred to as no infection or may logically be based on the truth that the infection's reasons perhaps anaerobic bacteria or viruses that usually could not be separated by the traditional culture approach utilized in this work. The heightened incidence of *E. coli* in UTI could be owing to the transferring of *Escherichia coli* from its natural environment in intestine (which is a part of micro-biota) and entry to the urinary system leading to infection [21].

3.3. Molecular Identification

3.3.1. Molecular Identification of Escherichia coli

Genomic DNA Extraction kit was used to get DNA from all of the isolates that passed the IMVIC test. (Figure 2) shows a gel electrophoresis run of the DNA samples. The outcomes showed that the concentration of all UPEC DNA samples was around 75 and 100 ng/l and the purity was between 1.7 and 1.9.

The extracted DNA was subjected to PCR to detect the uidA gene (encoded by all *Escherichia coli* strains) and used as a molecular identification target. The results revealed that this uidA gene was detected in all 84 isolates (100%) and gel electrophoresis was performed for laddered (100-1500 bp) PCR products as described in (Figure 2), (L = 100 bp DNA ladder, C = control negative, lanes (1-18): positive for the uidA gene (75 bp).

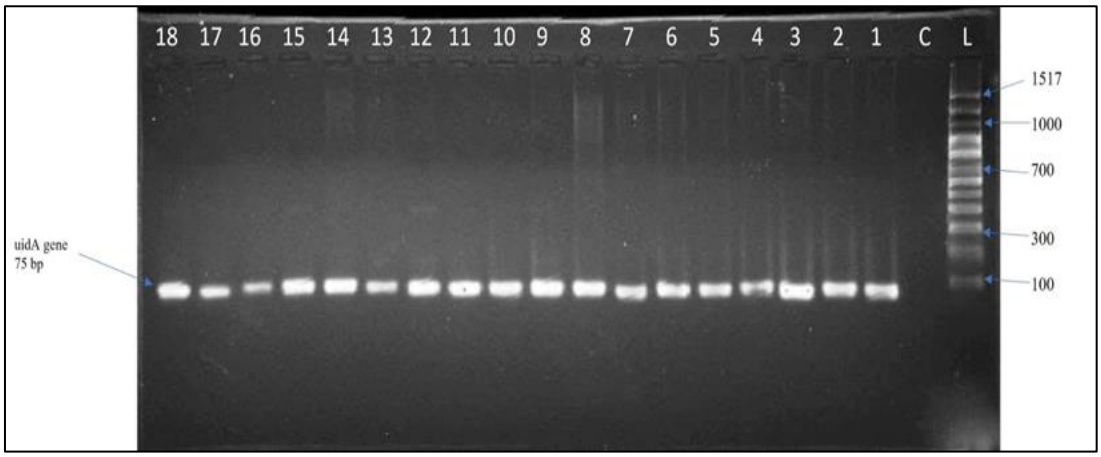

Figure 2 Gel electrophoresis for PCR products which were positive for uidA gene in all isolates of *Escherichia coli*

3.4. Molecular Detection of FimH gene

All extracted DNA that were used for detection of *Escherichia coli* were subjected to PCR by using special primer to detect FimH gene in *Escherichia coli*. In the present work, the outcomes revealed that FimH gene had been detected in all E. coli isolates, and gel electrophoresis was done for the products of PCR with ladder (100-1500 bp), as (figure3)shown. Lanes (1-18) are positive for the FimH gene (L=100 bp DNA ladder, C=control negative (164bp).

Figure 3 Gel electrophoresis for PCR products that was positive for FimH gene in *Escherichia coli* (164) bp ,(L= 100 bp DNA ladder, C = control negative , lanes (1-18):Positive for FimH gene (164bp) and lanes).

The link between fimH genes and urinary tract infections may be attributable to its crucial involvement in colony formation and uropithelial cell membrane adherence [27] .

The current study revealed that fimH gene that encodes Type 1 Fimbriae was current in all isolates of *Escherichia coli* and it was the most predominant gene among other adhesion-encoded gene, the result of current study in accordance with results of many studies [22] likewise reported that (100%) of isolates carried this gene [23] but [24] and [25]) revealed that the percentage of detected fimH was (92%) of fimH positive isolates and this slightly differences may be due to difference in the numbers of the studied samples , while [26] confirmed this the fimH gene stood the second prevalent adhesion-encoded gene among other virulence genes (73.1%).

3.5. Comparison The Levels of (IL-6) among Study Groups

The average level of IL-6 in the healthy control collective was (71.63±10.69) (pg/ml), while the mean rate in the non-diabetes collective was (100.60±15.4) (pg/ml) and the mean rate into the diabetes collective was (148.70±73.81) (pg/ml) (Figure 4).

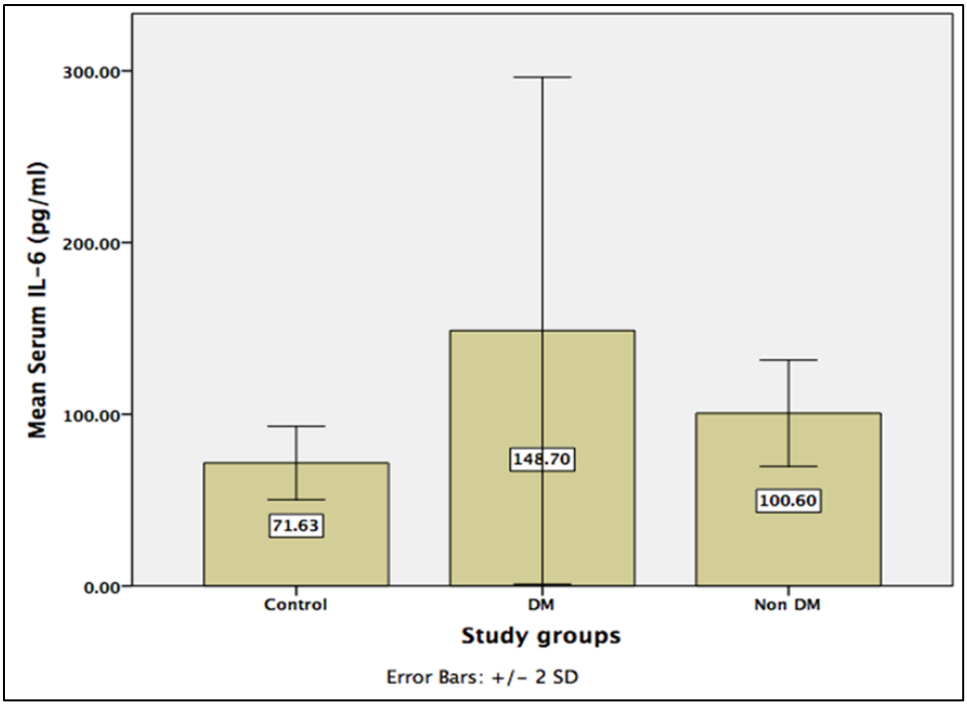

Figure 4 Comparison the levels of (IL-6) among study groups

(Table 8) showed highly significant distinctions in the means of IL-6 among studied group. The highest mean was in DM group, followed by the mean of Non-DM group and the lowest mean was in control group.

Table 8 Comparison the Levels of (IL-6) among research Groups

Groups	Mean of IL-6 (pg\ml)	Standard deviation	P value
control	71.63	10.69	< 0.001
DM	148.70	73.81	
Non-DM	100.60	15.47	

The average of IL-6 in Non-DM group has been high comparing with its mean in control group. Many studies agreed with these results. [28] showed that the levels of IL-6 and IL-17 in the blood of UTI-infected sufferers with E. coli that was positive for some virulence genes (including the FimH gene) were significantly higher than in healthy people who were not infected , also [29] showed that urine and serum concentrations of IL-6 and IL-8 were elevated considerably ($p<0.00$) in UTI women infected by E coli compared to controls. In fact, the rise in cytokines is due to their role in infection. In order to get pass the mucosal barrier, UPEC needs to express some of its virulence factors. Type I fimbriae is an infectious agent in the colonization of the host through UPEC, and it is engaged in disease of the urinary system. Bacteria into the upper urinary system move by flagella, which are mobile components of UPEC [30] On the other hand, In order to stop UPEC from colonizing and persisting, the host immune system employs a number of different strategies. Furthermore raised levels of IL-6 might induce the increase of TLR4 expression resulting in elevated local cytokines. Because activation of TLR4 by microbial virulence factor of UPEC, leading to increase transcription of IL-6 via energizing of Nuclear aspect kappa binding (NF-κβ), results in a rise across output of pro-inflammatory mediators, including cytokines and chemokines [31]. Some White Blood Cells (WBCs) make cytokines that act as chemoattractants to bring neutrophils toward injury area and regulate the host's defence opposing pathogens, which causes these cytokines to increase. Some of these cytokines are IL-6, IL-8, Monocyte Chemoattractant Protein-1 (MCP-1), C-C Motif Chemokine Ligand 5 (CCL5), TNF-, Gamma [32]. The result also showed that patients in DM group had levels of IL-6 more elevated compared with other groups, and there were considerable discrepancies among levels of IL-6 in DM patients group and non-diabetic patients (control group and Non-DM group); one recent studies have suggested that the glycated Hemoglobin was related to IL-6 levels [33]. Another recent study also found a link between a patient's blood glucose level and their levels of IL-6, TNF-, and IL-1, and a link between their levels of CD4+/CD8+ and their levels of IL-6, TNF-

, and IL-1 [34]. The effect of diabetes on IL-6 levels may be because DM can lead to a number of complications. One of these complications is the production of reactive oxygen compounds (ROS) through oxidation and phosphorylation reactions by enzymes. As hyperglycemia keeps going up, this activates Nuclear Factor-B (NF-B), which makes more pro-inflammatory cytokines (TNF-, IL-1) come out of the cells. Also, these cytokines have autocrine impacts that cause other cytokines, such as IL-6, to be made. IL-6 is a type of intermediate cytokine that has two different employment. First of all, when there is inflammation, pro-inflammatory cytokines like IL-6 are made more of. The second thing IL-6 does is tell other macrophage and neutrophil cells to make cytokines that fight inflammation [35] .

4. Conclusions

The study concluded that fimH gene was highly prevalent in *E. coli* isolates among diabetic patient with UTIs and presence of Type 1 fimbriae in UPEC strains which mediated the adherence ability of *E. coli* strains to the uroepithelial cells that result in increase of *E. coil* pathogenicity. Additionally, there was relation between diabetic patient with UTIs and interleukin 6 in this study.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed

Statement of informed consent

informed consent was obtained from all individual participants included in the study.

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